Workshop on Behavior-Based Donor Deferrals in the Era of Nucleic Acid Testing (NAT)

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FDA's Current Recommendations on Behavior-Based HCT/P Donor Deferrals

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Why are we discussing HCT/P donors today?

- HCT/P=human cells, tissues, or cellular or tissue based products
- Any change to blood donor suitability policies may affect HCT/P donor eligibility policies
- Currently, there are differences between blood donor and HCT/P donor policies on behavioral risk
- HCT/P donor types:
  - Cadaveric donors—cannot do follow-up
  - Living donors—can do follow-up if donor is available; test/quarantine/re-test/release---an option for some HCT/Ps

History of Regulation of Human Tissue for Transplantation

- 1985—CDC recommendations to test for HIV-1 in organ, tissue and semen donors
- 1992—report in NEJM of transmission of HIV-1 (4 organ recipients; 3 fresh-frozen bone recipients) from a screened, seronegative organ and tissue donor
- PHS Working Group—PHS and external consultants
- CDC Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissue and Organs—MMWR 1994;43(No. RR-8)

’94 CDC Guidelines

- Apply to donation and transplantation of human organs and solid tissues; general guide for human breast milk and semen
- Factors considered in developing guidelines:
  - Living (organ) vs. cadaveric donors (tissue)
  - Time constraints on viability (organ, cornea vs. bone)
  - Differences in risk of transmission (vascularized organ vs. avascular tissue)
  - Limited availability of organs
  - Benefit of transplant to recipient (organ—life-saving; tissue—usually life-enhancing)

**Despite recognition of these factors, it was too complex to stratify behavioral exclusionary criteria

’94 CDC Guidelines-- Behavior/History Exclusionary Criteria

- **Men who have had sex with another man in the preceding 5 years**
- **Persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years**
- **Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrate**
- **Men and woman who have engaged in sex in exchange for money or drugs in the preceding 5 years**

Continued

- Persons who have had sex in the preceding 12 months with any person described above or with a person known or suspected to have HIV infection
- Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin, or mucous membrane
- Inmates of correctional facilities
- Children 18 months or younger, born to mothers with or at risk for HIV infection, or who have been breast fed in past 12 months

FDA Regulation of HCT/Ps

- 1993—Interim Rule
  - Screen and test donors for HIV-1, 2; HBV; HCV; written procedures; records; inspections
- 1997—Final Rule
- 1997---Guidance
  - Behavioral deferrals for HIV, HBV, HCV, based on ’94 CDC Guidelines criteria**
  - Clinical evidence of HIV, HBV, HCV
  - Physical evidence of HIV, hepatitis

Continued

- **1997—Proposed Approach to Regulation of Human Cellular and Tissue-Based Products**—broader scope
- **2001—Registration and Listing Final Rule**
- **2004—Donor Eligibility Final Rule**
  - **Screen and test for HIV-1, 2; HBV; HCV; syphilis; others for specific types of tissue**
  - **Screen for TSEs, including CJD and vCJD**
- **2004—Draft Donor Eligibility Guidance**
  - **Added screening for WNV, SARS, Vaccinia, Sepsis**
- **2004—Current Good Tissue Practice (CGTP) Final Rule**—manufacturing controls

Consultation—June 2000

- Should ’94 CDC Guidelines be revised?
  - Review of incidence and prevalence data in high risk groups
- How much benefit (increased donor pool) would be seen vs. how much additional risk (release of infectious product) would be introduced?
- More studies needed; current data did not support the identification of “safe” subsets

FDA's Draft Donor Eligibility Guidance--2004

- Retained 1997 deferrals; continued to follow '94 CDC Guidelines
- Some changes from 1997 guidance:
  - Sex or other close contact in preceding 12 months with any person having clinically active hepatitis
  - Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after age 11, unless evidence from time of illness documents that hepatitis was identified as HAV
  - Added exclusions for HIV-1 group O, CJD, vCJD, WNV, SARS, vaccinia, sepsis, xenotransplantation

Limited Uses of HCT/Ps from Ineligible Donors, based on behavioral risks, clinical or physical evidence, or reactive tests

- Allogeneic use in a first-degree or second-degree blood relative
- Directed donor of reproductive cells/tissue
- Documented urgent medical need (no comparable cell/tissue is available and the recipient is likely to suffer death or serious morbidity)—e.g., HLA-matched hematopoietic stem cells
- Requires special labeling and physician notification

Incidence and Prevalence of HIV, HBV, HCV, and HTLV among U.S. Tissue Donors

Zou et al. Probability of Viremia with HBV, HCV, HIV, and HTLV among Tissue Donors in the United States. NEJM;351:751-759

- **2000-2002--11,391 donors—5 tissue banks—confirmed positive test results→marker prevalence rate**
- **Estimated incidence rate and estimated probability of viremia for HIV, HBV, HCV, HTLV**
- **<u>Conclusion</u>: Prevalence and incidence rates are lower among tissue donors than in the general population, but higher than in first-time blood donors.**

Marker/ Type of Donor	Prevalence=# Confirmed Positive/Total (%)	Estimated Incidence (per 100,000 person-years)	Estimated Probability of Viremia (serologies only)
HIV Antibody— 1st time Blood	0.010	2.43	
HIV Antibody— Tissue	**0.093**	**30.118**	**1 in 55,000**
HIV Antibody— Gen. Population	0.20	15	
HBsAg— 1st time Blood	0.077	2.50	
HBsAg— Tissue	**0.229**	**18.325**	**1 in 34,000**
HBsAg— Gen. Population	0.42	69	
HCV Antibody- 1st time Blood	0.304	2.42	
HCV Antibody- Tissue	**1.091**	**12.380**	**1 in 42,000**
HCV Antibody- Gen. Population	1.80	14	

Behavioral Deferrals—HCT/Ps Rationale

- More reliable answers to the donor history questionnaire if questions pertain to the recent past (e.g., in the past 5 years vs. since 1977)
  - when the donor himself is not being questioned, but instead, the next-of-kin
- Limited availability of certain cells/tissue
  - Need for HLA-matched cells (e.g., hematopoietic progenitor cells)
  - Size restriction for pediatric tissues (e.g., heart valves)
- Differences in risk of viral transmission due to more extensive processing of some types of tissues
  - Removal of blood and viable cells by extensive washing, use of isopropanol, hydrogen peroxide, irradiation, and proprietary methods for viral clearance

Additional Information about FDA Regulation of HCT/Ps

- www.fda.gov/cber/tiss.htm
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